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Mastopathy and breast cancer

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Summary

Mastopathy (*mastopathia fibroso-cystica*) and breast cancer are two major epidemiologic, economic and medical problems of women. In Poland, annually, 0.2-1.6 billion Polish zlotys is spent on diagnosis and treatment of mastopathy; half of that sum is spent improperly. Many papers suggest relationships between these two diseases, however, it is not certain, whether, or how much, mastopathy increases breast cancer incidence. The available papers from the recent years indicate increased risk, but the methodology of these data is not perfect. It is not excluded that fibrocystic diseases of the breast increase breast cancer incidence. If such an influence exists, independent of other well-know factors, it is probably very small. Moreover, due to the diversity of medical information there is a lack of diagnostic and therapeutic standards in mastopathy. Different types of scans, hormonal, biochemical and immunohistochemical examinations are performed improperly, and there has been no genetic analysis of mastopathy. Therefore, there is a strong need of well-planned, prospective trials in this field.

Key words: mastopathy • breast cancer

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Terminology

Mastopathy is a medical term very frequently encountered by doctors and female patient. A "key word" intended to facilitate the communication between the doctor and the patient, which, however, often makes it more difficult. So, what is mastopathy? If we type in this word in the most popular web browser service (www.google.pl), we get 645 Polish websites containing this term. We can read there, among others, that:

„Mastopathy, degenerative changes in the tissue of mammary glands, due to hormonal disorders. They usually take the form of nodules or indurations, which always require specialist control and diagnostic examinations (USG, mammography, biopsy) to be differentiated from malignant lesions" [1];

„The first step after detection of cyst-like lesions, which frequently result from chronic hormonal disorders, is testing blood hormone levels, especially those of ovarian hormones (estradiol, progesterone, testosterone), pituitary hormones (prolactin, luteotropic hormone follicle stimulating hormone) thyroid ones." [2];

„It should be remembered that mastopahy can increase the risk of breast cancer and that breast cancer can develop among mastopathic lesions. It should be remembered that a tumor may arise both from small cyst-like lesions and from large cysts!" [3];

„As a rule, cysts develop in women above 30 years of age, very often immediately before menopause. They rarely develop in postmenopausal period and in very young women. Fine needle biopsy is necessary to confirm the diagnosis" [4];

„Wearing bras is not necessary, and even contraindicated. Bras impair vascular function, especially that of lymphatic vessels within the breasts, which may lead to an increased risk of breast cancer" [5];

„USG can detect, for example, benign pathologic changes in the bust (mastopathy). Such mastopathy, with no malignant lesions, occurs especially in young women. The causes may be varied: familial predisposition, hormonal disorders, changes in breast tissue caused by premature suppression of lactation, or inflammatory conditions of the breast" [6].

The above examples illustrate how many misunderstandings (and even inappropriate actions) may be caused by such information.

If we, in turn, type in the English word (mastopathy) in the most popular professional medical browser www.pubmed [7], only 72 medical publications from the recent decade containing this word in the title are displayed. During that period, 60 papers concerning diabetic mastopathy were published, and only 12 concerning fibrocystic breast mastopathy, including only 1 publication written in English. It is worth remembering that diabetic mastopathy is a rare glandular hyperplasia of fibrous breast tissue, which develops in the course of long-lasting type I diabetes.

Does that mean that mastopathy is a term used (in medical or popular scientific publications) only in Poland or in East Europe? This is probably the case, because English scientific literature more often uses the term "benign breast diseases" (BBD). However, the meaning of these two terms is not identical. *Mastopatia fibroso-cystica*, as indicated by the term itself, may contain fibrous, inflammatory and cystic elements, and that is why a synonym "fibrocystic degeneration" is often used. According to some Polish pathologists, the lesions of *hyperplasia nonatypica, adenosis (nonsclerosing)* and *ductectasia* may also be components of mastopathy. On the other hand, the College of American Pathologists (CAP) lists the following pathologic conditions, which can be collectively referred to as BBD [8]. The College specifies also which of these conditions, and to which extent, increases the risk of breast cancer (BC) – tab. 1.

It seems that this important table could conclude the present considerations, but…. .

Epidemiology and economics

All physicians dealing with breast diseases know that mastopathy and BBD are very frequent. Although there are no precise epidemiological data, many publications contain information that benign lesions of various type are found in 30–50% of women. On the other hand, autopsy studies indicate that cysts and cyst-like lesions are found in 75% of autopsied women. In my opinion, the problem of mastopathy and BBD concerns all women and is of more qualitative than quantitative. Some pathology would probably be found in every woman on thorough pathological examination of the breasts. Similarly, there are no subjects without any pathology of the skin.

The lack of epidemiological data from screening tests makes it necessary to use various simulations. On the basis of a large-scale study conducted in the group of 265,402 women working in Shanghai clothing industry, we know that symptomatic (clinically palpable) fibroadenomas frequency amounts to 600/1,000,000 examined women. On the basis of that [9] and other studies, the risk of developing a fibroadenoma during the whole life can be estimated at 5% to 30%. According to another paper, based on the analysis of 11,307 women, the incidence of category 1 and 2 BBD (tab.1) was determined at 12.2% of female population. In that study, fibroadenomas accounted for 12% of lesions presenting as a tumor or induration, so, combining the above data, it can be assumed that the frequency of various indurations amounts to 5% (annually).

In addition to estimation of the epidemiological data, the economic aspect of the problem is also worth considering. Out of 20 m women in Poland, 10% to 20% undergoes breast examinations of various type. If expenses of

Table 1. Benign breast diseases (BBD) and the risk of breast cancer according to the College of American Pathologists.

Category	*Breast cancer risk level*	*Pathology*
1	Not increased	*Adenosis* (other than *sclerosing adenosis)* *Ductectasia* *Fibroadenoma* *Fibrosis* *Mastitis* Mild non-atypical hyperplasia Simple micro- or macro-cyst Simple apocrine metaplasia Planoepithelial metaplasia
2	Slightly increased	Fibroadenoma (with coincident so-called complex features) Moderate/extensive non-atypical hyperplasia *Sclerosing adenosis* Papilloma without atypical hyperplasia
3	Moderately increased	*Atypical ductal hyperplasia* *Atypical lobular hyperplasia*
4	Significantly increased	*Ductal carcinoma in situ* *Lobular carcinoma in situ*

diagnostics in each individual case (clinical examination, USG, mammography, biopsy, hormonal investigations and other tests) fall, on the average, within PLN 100–400 range (payable from all sources) it can be presumed that annual expenses reach about a billion zlotys (range from 200 m to 1.6 bn). It is the amount comparable to the annual budget of all the oncology centers in Poland.

Risk factors for breast cancer

So-called classic breast cancer risk factors [10], in Gail model applicable since 1989, include:

- early menarche
- late menopause
- late first pregnancy (childbirth)
- familial occurrence of breast cancer
- previous biopsies or surgical procedures performed on the breast

In 2006, the US National Cancer Institute (NCI) added new parameters associated primarily with introduction of mass scale mammographic screening [11, 12]:

- high mammographic breast tissue density
- high BMI (body mass index)
- hormonal replacement therapy (HTR, especially E+PR)

At NCI website [13], a tool enabling to calculate the risk of breast cancer in an individual patient according to the risk factors present, so-called „BC RISK CALCULATOR", can be found. Tab. 2 presents in 2 columns the examples of 2 different women with the risk of breast cancer calculated for either patient.

Additionally, it can be calculated that the risk of developing breast cancer by 90 years of age reaches even 44.8%, so it is 4-fold higher than the mean risk in the population of white 50-year-olds – 11.2%.

Wang published in 2004 an important study [14], which indicates that the risk of developing breast cancer among women classified as category 1 or 2 – so-called LC-BBD (tab. 1) was 1.6-fold higher than in BBD-free population. On the basis of analysis of 11.307 women, including 1376 with LC-BBD (47 developed BC – 3.4%) and 9931 without LC-BBD (291 developed BC – 2.9%) the differences were assessed to be significant and independent of other risk factors (Gail model). Differences within the LC-BBD group were also compared by the author, who concluded that the relative risk (RR) of developing breast cancer among women with cyst-like breast lesions is 1.79 (95% CI 1.20-2.68) and is significantly higher than in other non-cystic LC-BBD, where RR amounts to 1.42 (95% CI 0.91-1.95). Thus, a conclusion based on the study can be made that all BBD, and cysts in particular, significantly increase the risk of breast cancer. However, such conclusions can arouse considerable objections, although they seem to be statistically correct. As it follows from the analyzed material, the risk of breast cancer among BBD-free women is 2.9%, among women with cysts 3.8% and among women with other types of LC-BBD 3%. Thus, can we speak about a significant increase of risk in case of differences ranging from 0.1 to 0.9%?

Even more doubts arise when we look more closely at the material presented in this study which originates from … another study [15], published 6 years before (P1 – BREAST CANCER PREVENTION TRIAL) and concerning a randomized clinical trial assessing prophylactic efficacy of tamoxifen in women with increased BC risk. The study analyzed 13,388 women (1992–97) with increased BC risk (RR>1.66%), receiving tamoxifen (6576) or placebo(6599). The results indicated that tamoxifen reduced almost by half the incidence of breast cancer, because 89 out of 6576 women (1.4%) developed BC in that group in comparison with 175 BC cases in the control group of 6599 women

Table 2. Example of breast cancer risk calculation in 2 women on the basis of risk factors – BC RISK CALCULATOR according to NCI.

Risk factor	Woman 1	Woman 2
History of breast cancer (including DCIS, LCIS)	NO	NO
Age	40	50
Age at the menarche	15	11
Age at childbirth	24	30
1st degree relatives affected with breast cancer	0	1
Number of previous biopsies or surgical procedures	0	2
Previous detection of atypical hyperplasia	NO	YES
Race	white	white
CALCULATED BREAST CANCER RISK DURING 5-YEAR PERIOD:	**0.6%**	**6.2%**

(2.7%). That study led to appropriate recommendations for women with increased risk of breast cancer. However, it is a pity that so many women (98.7%) used (or still use) tamoxifen unnecessarily, because it provides favorable protective effect only in 1.3% of the treated patients.

Coming back to Wang's study, another important question arises: Can an additional risk factor be assessed (post factum) in a group of patients with generally increased risk? And should a study of 2004 have been based on material collected for a different purpose in 1992–97?

Other recent studies [16–20], suggesting a correlation between benign breast diseases and the occurrence of breast cancer, are even weaker in the methodological and statistical aspects.

In turn, Hartmann [21] analyzed in in 2005 a group of 9087 operated on for benign breast lesions (in 1967–91), among whom 707 (7.8%) developed breast cancer (10 years later, on the average, including 40% of cases in which the contralateral breast was affected). The group, assessed with respect to age, relation to menopause and histological type of the lesion, was compared epidemiologically to the control population in Iowa. The resected lesions were divided into three histopathological types:

I – non-proliferative fibrocystic lesions – 67%,

II – non-atypical proliferative fibrocystic lesions – 30% and

III – atypical ductal or lobular hyperplasia – 4%.

The breast cancer risk for all lesion types was estimated to be 1.56-fold higher than in the control population (group I = 1.27, II = 1.88, III = 4.24). However, the authors emphasize that mastopathic lesions (group I, II) in patients without high familial risk (mother or sister below 50 years of age or two women in the family including one next of kin) did not increase the frequency of breast cancer.

These problems have also been assessed from another point of view [22] by Collins (a case-control study). On the basis of 2005 women with BBD including 395 (19.7%) who developed breast cancer, the effect of positive family history (FH+) on breast cancer risk according to the histological type of previously removed lesion (classified as above) was assessed. In comparison with type I BBD without positive family history, the risk of developing breast cancer was: 1.51 for type II BBD FH-, 2.45 for type II BBD FH+, 4.38 for type III BBD FH- and 5.37 for type III BBD FH+. Thus, positive family history slightly but significantly increased the risk of breast cancer for type II BBD and insignificantly increased the risk of breast cancer for type III BBD.

Chun [23], on the basis of 1317 women with high breast cancer risk (including 28% with large cyst-like lesions) did not confirm the hypothesis that the presence of cysts in the breast is a significant risk factor for developing breast cancer [23].

Conclusion

It cannot be excluded that fibrocystic lesions increase the risk of breast cancer. Such influence, even if existing independently of other risk factors, is fortunately low. Despite the publication of reports [24] concerning favorable effect of aspirin (by cyclooxygenase inhibition) on reducing the risk of breast cancer in women with benign breast diseases (mastopathy and/or BBD), further studies are necessary to elucidate potential correlations (and, first of all, their magnitude) between the incidence of mastopathy and breast cancer.

The aim of such studies should be comparative analysis of molecular, pathological, hormonal, biochemical and imaging investigations in a group of patients with mastopathy (only) and in a group with coincident mastopathy and breast cancer. The analysis of results should answer the following questions:

How frequent are mutations in the analyzed groups?

What are the characteristic features of mastopathy and breast cancer in the analyzed examinations?

What examinations can be predictive of breast cancer in mastopathy?

What should be the algorithm of mastopathy management?

Systematic knowledge and standardization of management in benign breast diseases should result in economic benefits, and indentification of women with high risk of breast cancer would allow early detection and most effective treatment.

Unfortunately, KBN (Polish Scientific Research Committee) did not approve in 2004 a multicenter study designed to assess objective correlations between mastopathic lesions and breast cancer (1500 patients – PLN 1,5 m = 0.1% of all costs incurred by mastopathy).

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